individual substances or in a mixture, hydrogenated fat, glycerol tri-fatty acid esters, glycerol trilaurate, -myristate, - palmitate, -stearate and -behenate, waxes, cetyl palmitate, cera alba and beeswax.

36. (Amended) Formulation according any one of claims 37 and 38 [1], wherein the particle size distribution of the spray-dried particles is between 1 and 630 μm [is such that] and 50 to 80% of the spray-dried particles are between 63 and 400 μm.

REMARKS

Reconsideration and allowance of the subject application are respectfully requested. Claims 9, 25 and 31-49 are pending in the application.

Basis for new claims 37-49 can be found in the present application. Further basis for new independent claims 37 and 38 can be found at cancelled claim 19. Further basis for new independent claim 44 can be found at cancelled claim 23. No new matter has been added.

The rejection claims 27-30 under 35 U.S.C. § 112, first paragraph, at paragraph 12 in the Office Action, is obviated by the cancellation of the language "time-release" from the pending claims. The claims have been amended to recite "prolonged-release," support for which can be found throughout the present application including at page 1, line 16.

According to well-established definitions, an oral dosage form classified as a "prolonged release" system should be able to release drug up to 5 to 8 hours (P.H. List, Arzneiformenlehre, Wissenschaftliche Verlagsgesellschaft, Stuttgart/Germany, page 457, 1976). The duration depends on the "quality" and "capability" of the release system. A good system should allow to modify its composition this way, that it can cover shorter periods but also a period of 8 hours release (or even more).

Figure 5 of the present specification demonstrates the capability of the invention to provide prolong release. After 8 hours (480 min on x-axis) only about 50% of the drug has been released. Plotting it as a function of the square root of time (Fig. 6 of the present specification) shows that it is a nice matrix release. In the

Figures, 50% of incorporated drug is released in the given time, the graph allows to calculate the theoretical maximum time for 100% release being not longer than 16 hours.

In general, most drugs are substantially absorbed in the small intestine, the passage time there is approximately 8 to 10 hours after ingestion. That means for most systems to deliver these drugs, a release time of 8 hours is sufficient. The last fraction released to the lumen of the intestine will be absorbed within the remaining two hours.

However, since some drugs show also absorption from the colon, for such drug systems a longer "prolonged release time" is desired.

For these reasons, Applicant submits that the claimed invention fully complies with Section 112. Accordingly, withdraw of the Section 112 rejection is respectfully requested.

The rejection of claims 1, 13, 15, 16, 19, 20, 23, 24, 26, and 31-35 under 35 U.S.C. § 102 over Chen is respectfully traversed. The claimed invention is not anticipated by Chen for the following reasons.

The spray-dried product by Chen is a microcapsule. A capsule is composed of a core and a surrounding wall (shell). The drug is coated with the polymer Eudragit L 30D in the spray-drying process leading to a capsule.

The prolonged release is achieved not by the compressed tablet, but by the microcapsules released after fast disintegration of the tablet. In contrast to this, the spray-dried Compound according to the present invention has no core/shell structure, e.g. compare Figure 1 in the present application, lower part.

The flowability of the powder by Chen is poor (column 3, lines 41/42; coulmn 6, line 19). In contrast to this, the compound according to the present invention has good flow properties.

The poor flow properties are clearly documented in Chen. Chen needed to add additives to promote the flow and to enable the mixture to be compressed by direct compaction. The flow promoting additives were flostarch and good flowing microcrystalline cellulose (column 5, lines 22-24). In addition, Chen had to add further flow additives, the classical aerosil. Normally aerosil is added in concentrations as low as 0.2% to 0.5%, however, Chen had to add 1.5% to obtain a good flowability (column 5, line 25).

In addition Chen added a relatively high amount of talcum, being primarily a lubricant but also a flow promoter.

Again, as in Bauer, the tablets of Chen rapidly disintegrated. This was due to the fact that highly water soluble additives were used in addition to lactose, i.e. PEG 6000 and soluble starch (column 4, Table I), i.e. a total of 58.75 % (25 %, 3,75% and 30 %, respectively).

The release principle of Chen is different to that of the present invention. According to Chen the tablets disintegrate and microcapsules are released, which create a prolonged release. In contrast, in the present invention prolonged release is achieved by maintaining the form of the compressed unit (e.g. tablet), the prolonged release is achieved by the polymeric network in the e.g. tablet (compare e.g. Figure 2 in the present application, lower part).

The examiner points out that identical compositions must have identical flow properties. This is not true because an identical chemical composition can have differences in physical parameters, e.g. structure, surface properties (charge, roughness) and size. This results in completely different properties for flow and compression. The particles by Chen are described such that the microstruture (Column 6, lines 14-18) and small size lead to poor flow properties. The microstructure of the present invention is different to that of the Chen product (**no capsule**, special structured particle), in addition the size is different. Chen has very fine particles (column 6, line 15), the present invention results in a particle size distribution of large particle, e.g. for the lactose/ethylcellulose compound ranging from 1-630 µm, 50-80% of the powder being typically between 63 µm and 400 µm. This shows that microstructure and size/size distribution differ.

For these reasons, the claimed invention cannot be anticipated by Chen. Accordingly, withdrawal of the Section 102 rejection is respectfully requested.

The rejection of claims 19, 21 and 23 under 35 U.S.C. § 102 over Bauer is respectfully traversed. The claimed invention is not anticipated by Bauer for the following reasons.

The present invention claims tablets produced from the "compounds" which do not disintegrate fast. The prolonged release is achieved because the compressed unit (e.g. tablet) preserves its form with no disintegration or very little erosion over a longer period of time.

In contrast to this, the tabletting agent used by Bauer leads to very fast degrading tablets (column 1, line 41; column 2, line 36). It is highlighted that the tablets have the hardness of a cellulose tablet but disintegrate similarly fast to a pure lactose tablet (e.g. column 4, Table-continued: 19 sec disintegration time of the Bauer formulation). Thus, Bauer teaches away from the present invention.

Bauer uses only cellulose, no derivatives. The reason for this is simple; Bauer wants fast desintegrating tablets. To enable this, Bauer teaches to use non-swelling polymer, that means simple natural cellulose. Cellulose is known for showing very little swelling (e.g. wet newspaper made from cellulose does not swell). Especially, Bauer teaches to avoid a swollen or dissolving polymer since it causes gel formation and stickiness, both delaying the fast disintegration of tablets – the aim of Bauer's invention.

Bauer especially uses normal cellulose powder (fibre cellulose), because microcrystalline cellulose forms hard binding forces in the tablet thus delaying the disintegration.

In contrast to this, the cellulose derivatives recited in claim 37 have a good swelling. Cellulose ethers are used to produce hydrocolloid matrix tablets. They are admixed to the powder and then granulated and compressed. The mechanism is that the cellulose derivatives swell leading to a swollen, non-disintegrating matrix with prolonged release. Therefore in the present invention, the cellulose derivatives provide different properties than cellulose.

For these reasons, the claimed invention is not anticipated by Bauer. Accordingly, withdrawal of the Section 102 rejection is respectfully requested.

The rejection of claims 1, 2 13, 15, 16, 19, 20, 22-26 and 31-35 under 35 U.S.C. § 102 over Norling is respectfully traversed. The claimed invention is not anticipated by Norling for the following reasons.

While the "consisting essentially of" language of claim 37 includes conventional additives such as lubricants and surfactants which do change the nature of the compound, it excludes the active drug. Norling requires the use of a drug as an integral part of his pellets. For this reason, Norling cannot anticipate claim 37.

Norling also does not anticipate the claimed invention for the following reasons. First, the chemical excipients presently used are very different from those used by

Norling. Norling inorganic salts are essential for the core of his units, whereas the present invention utilizes polymers and other organic compounds.

Norling discloses a coated drug-free core, achieved by using large inorganic, drug-free cores with a size up to 225 µm. These cores are then coated. That means there is an uneven distribution of drug. The center is drug-free, the drug located in the shell.

In contrast, the invention has an even distribution of drug particles throughout the complete particle matrix, when the claimed compound is mixed with the active ingredient (drug). See Fig. 4, middle right and lower right in the present application.

Secondly, while Norling and the present invention both use spray-drying, using the same spray-drying does not automatically result in identical products. Spray-drying is used in technology to produce very different pharmaceutical for-mulations (e.g. hollow beads of solid solutions, solid dispersion particles, instant powders of plant extracts). From this, it is clear that one and the same method can lead to very different products. Different products can even be achieved when using the same excipients. Thus, the product structure can also be controlled by production and plant and processing parameters. Especially, there are different products when different excipients are used.

Applicant respectfully submits that the Examiner is not correct stating that the same ingredients are used. Inorganic salts are essential for Norling's formulation, whereas they are not required in the invention.

It is correct that Norling uses a polymer as used in the present invention and many other pharmaceutical products, but this does not necessarily mean that these two products are identical. In Norling, the polymer is, e.g., used for coating the calcium carbonate core (example 1A). In example 2 for drug-loaded pellets, calcium carbonate, drug and the polymer PVA is used.

For the pellets, Norling does not use a compound composition polymer plus at least one other soluble excipient.

Apart from this, the structures are clearly different:

pellet - coated calcium salt core (Norling), i.e. continuous core phase and the polymer coat is also continuous.

Compound – two-phase matrix particle with coherent phase of e.g. lactose and the polymer dispersed as particles in this matrix (non-coherent phase) (present invention).

The terms "pellet" and "compound" are well defined in the technical literature and also in textbooks. Therefore using the term "compound" in the present claims distinguishes the invention clearly.

There are very clear definitions of pellets in the literature. One way to produce pellets is using a drug-free core (so called nonpareille) and adding layers on it applying different methods. This is exactly what Norling is doing, a core-shell structure.

The term compound does not include the pellets produced by coating of cores, and, thus, the claimed invention does not cover the Norling systems.

To explain the difference, Applicant refers to the definition given in the chemical dictionary "RÖMPP Chemielexikon", Thieme Verlag, Stuttgart /Germany, 9 edition paperback, 1995, volume 5 (PI-S), page 3545:

> Polymer compounds are processing-ready mixtures of polymers with other additives, additives being e.g. anti-aging substances, antioxidants, fillers (in case of the invention e.g. sugars), and plasticisers, the compounds to be used as intermediate product to produce the final product.

This is a very general definition valid for all chemical, food and so on processes. In the pharmaceutical field it is more defined to pharmaceutical needs, also considering the type of final product and consequently the properties a compound needs to possess. It covers powders being:

a) only an intermediate product to produce the final dosage form, they are not intended to be used on their own;
b) the final dosage forms are e.g. tablets;
c) there is no specific structure described for polymer compounds, i.e. it is a non-ordered structure (e.g. like the present invention); and
d) the shape is not defined.

Looking strictly to the words of the definition, one could consider a pellet being a polymer compound because the compound definition is very general, however: In pharmaceutical terms, drug formulations like pellets are special systems, which - from the historical development - are outside the definition of compounds because the pellets represented a final dosage form since their invention (Pierre Pelletier, 1788-1842). This has changed a few years ago when somebody used the pellets to compress them to a tablet (e.g. Beloc ZOK, also described by Norling). However, these new kind of processing did not lead in practice considering pellets now being a compound. There is still a valid distinction between pellets (Norling) and a compound (claimed invention).

Norling prepares tablets from the pellets (example 11). It should be noted that this is a well known procedure. This procedure is clearly different to the invention.

According to Norling, pellets are mixed with 60% to 80% other excipients (e.g. binders as Avicel) to yield a compressible mixture leading to stable tablet.

The speciality of the compounds according to the present invention is that they do not need to be mixed with binders such as Avicel, they can be compressed directly. The tablet comprises primarily 100% compound (when ignoring the necessary lubricant (e.g. 0.5%) for the tablet machine).

Again, the two tablets are different. In Norling pellets are dispersed in the matrix of the tablet (cf. enclosure – upper figure, from Müller, R.H., Hildebrand, G.E. (eds), Pharmazeu-tische Technologie: Moderne Arzneiformen, Wissenschaftliche Verlagsgesellschaft Stuttgart/Germany, 1997) - copy enclosed and disclosed on the attached herewith FORM PTO/SB/08B. Please sign and date the enclosed FORM PTO/SB/08B and return a copy to the undersigned. Each pellet has a core – coat

structure (cf enclosure, lower figure) and the pellet includes the drug.

According to the present invention the claimed tablet is a unit with homogenous excipient (e.g. lactose phase) with polymer particles and separate drug particles dispersed therein (Fig. 2 of the present invention).

The ingredients used by Norling and according to the present invention are different. Even the process is similar (spray-drying), this does not lead to the same product. Clearly structural differences are documented, pellet versus Compound.

The Rule 132 Declaration of record also demonstrates the differences between Norling and the claimed invention, as discussed more fully below.

For these many reasons, the Section 102 rejection should be withdrawn.

The rejection of claims 1, 2, 9, 13, 15, 16, 19-26 and 31-35 under 35 U.S.C. § 103 over Norling in view of Bauer is respectfully traversed. The claimed invention is not taught or suggested by the theoretical combination of Norling and Bauer for the many reasons of record, the many reasons provided herein above, and for the following reasons.

One of ordinary skill in the art would not be motivated to look to Bauer when trying to produce a prolonged-release formulation according to the present invention. Bauer teaches in a direction opposing the claimed invention since he teaches a quick release formulation, as discussed above. For this reason alone the Section 103 rejection should be withdrawn.

Norling does not provide the deficiencies of Bauer. As discussed above, Norling teaches to form pellets having a drug free core on which layers are provided. A tablet is provided by dispersing the pellets in a matrix. Combining this teaching with Bauer, one does not arrive at a "compound" formulation according to the present invention that does not contain pellets according to Norling. Furthermore, Norling teaches a very different release system than the claimed invention, for the many reasons provided above. Thus, the combination of Bauer and Norling also must teach this different release mechanism. There is no combination of Bauer and Norling that teaches a prolonged-release formulation according to the present invention, i.e. without use of coated pellets.

In view of the improper combination of reference, and the differences between the claimed invention and the theoretical combination of references, withdrawal of the Section 103 rejection is respectfully requested.

Applicant respectfully submits that the Rule 132 Declaration submitted on March 1, 2002 demonstrates the patentable distinctions between Norling and the claimed invention. See page 5 of the Declaration, which states that:

> "The same described or Lang is valid for Norling. Norling also uses membranes (coated cores = membrane around drug core). There is no principle difference between coated tablets and coated pellet, just the size and form of the unit. It should be pointed out that the systems [(the present invention and Norling] lead to the same result (i.e. prlonged release), but this does not mean they are necessarily identical. To illustrate it from practical life: I can use a mean of transportation to go from Washington DC to LA, e.g. a train or a plane. They are both means of transportation (in case of patents "prolonged release units") but nevertheless they are different.

Thus, the Declaration clearly points out the distinction between the pellets of Norling and the compound according to present invention.

On page 10 of the pending Office Action, the Examiner argues that the features relating Higuchi law and Fick law are not part of the present claims nor evidentiary based. Applicant respectfully disagrees. Page 4 of the Declaration clearly states that "Muller [present invention] describes release from a matrix system, release takes place by the Higuchi law." The Higuchi law is an inherent property of the claimed "compound," i.e. how the claimed formulation in the form of a compound provides prolonged release by releasing from a matrix according to Higuchi law.

In contrast, page 4 of the Declaration also states that "Lang is using a membrane surrounding the compressed drug. This can be compared with drug release from a dialysis bag, it releases after the Fick Law." The Fick law is merely used to illustrate how the membrane of Lang releases. The Declarant also stated that the pellet structure of Norling also releases like Lang according to the Fick law. See page 5 of the Declaration.

The Hick law and Fick law are merely inherent properties of the claimed compound and Norling's pellet, respectively. It is clearly proper for Rule 132 Declaration's to document such properties, which demonstrate patentable subject matter.

Thus, the Declaration clearly describes the patentable differences between the coated pellets of Norling (which have the inherent property of releasing according to the Fick law) and the presently claimed compound (which has the inherent property of releasing according to the Hick law).

Applicant respectfully requests that the Examiner give full and fair consideration to the Rule 132 Declaration and arguments provided above, which clearly demonstrate the patentable distinctions between the pellets of Norling and compound of the claimed invention.

In view of all of the objections and rejections of record having been addressed, it is believed that the present application is in condition for allowance and Notice to that effect is respectfully requested.

Respectfully submitted,

Jeffrey S. Melcher
Reg. No. 35,950
Tel: 202.261.1000
Fax: 202.887.0336

Customer No. 20736